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Date: 18 November 2008

N. T. SIMPKIN
Deputy Managing Director - UK Translation Division
For and on behalf of RWS Group Ltd

[crest]

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File Reference **A 585/2003**

The Austrian Patent Office herewith certifies that

BIOCHEMIE GmbH

of A-6250 Kundl/Tyrol

(Tyrol),

filed a patent application on the **16 April 2003**

relating to

"Organic compounds",

and that the attached description entirely agrees with the original description filed simultaneously with this Patent Application.

Austrian Patent Office
Vienna, 11 March 2004

The President
pp
[Stamp of the Austrian Patent Office]
[signature]

HRNCIR
Senior Technical Inspector

[Seal of the Austrian Patent Office]

A 585/2003

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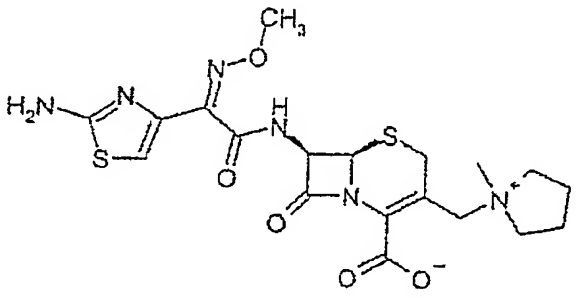
Organic compounds

The present invention relates to the preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxy-imino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate). Cefepime is a valuable 4th generation injectable cephalosporin with antibacterial properties, see e.g. The Merck Index Thirteenth Edition, Item 1935.



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The preparation of cefepime is not simple. For example, it is known that the 7-acyl side chain as the difficult-to-obtain 2-(2-aminothiazol-4-yl)-2-methoxy-imino-acetic acid chloride hydrochloride must be used for the production of cefepime, in order to obtain an active ingredient which is pure in respect of the by-products anti-isomer and Δ-2 isomer.

A novel process has been found which solves the abovementioned problems.

In US patent 4,266,049, a 7-acyl-3-acetoxymethyl-cephalosporinate is converted with the assistance of an iodotrialkylsilane into the corresponding persilylated 3-iodomethyl compound and this then undergoes nucleophilic substitution in the 3'-position. This technology can only be applied to the production of

cefepime - starting with cefotaxime - to an uneconomical extent, since N-methylpyrrolidine as a strong base can greatly induce the formation of the by-products Δ-2 und und 7-epi (Walker et al, J.Org Chem. 1988, pages 983-991).

The present applicants found that working with N-methylpyrrolidine - trialkylsilane adducts iodotrimethylsilane and N-methylpyrrolidine as described in the above literature led to unsatisfactory results when using cefotaxime as the starting material.

Surprisingly the synthesis from cefotaxime is achieved by the following formula scheme:

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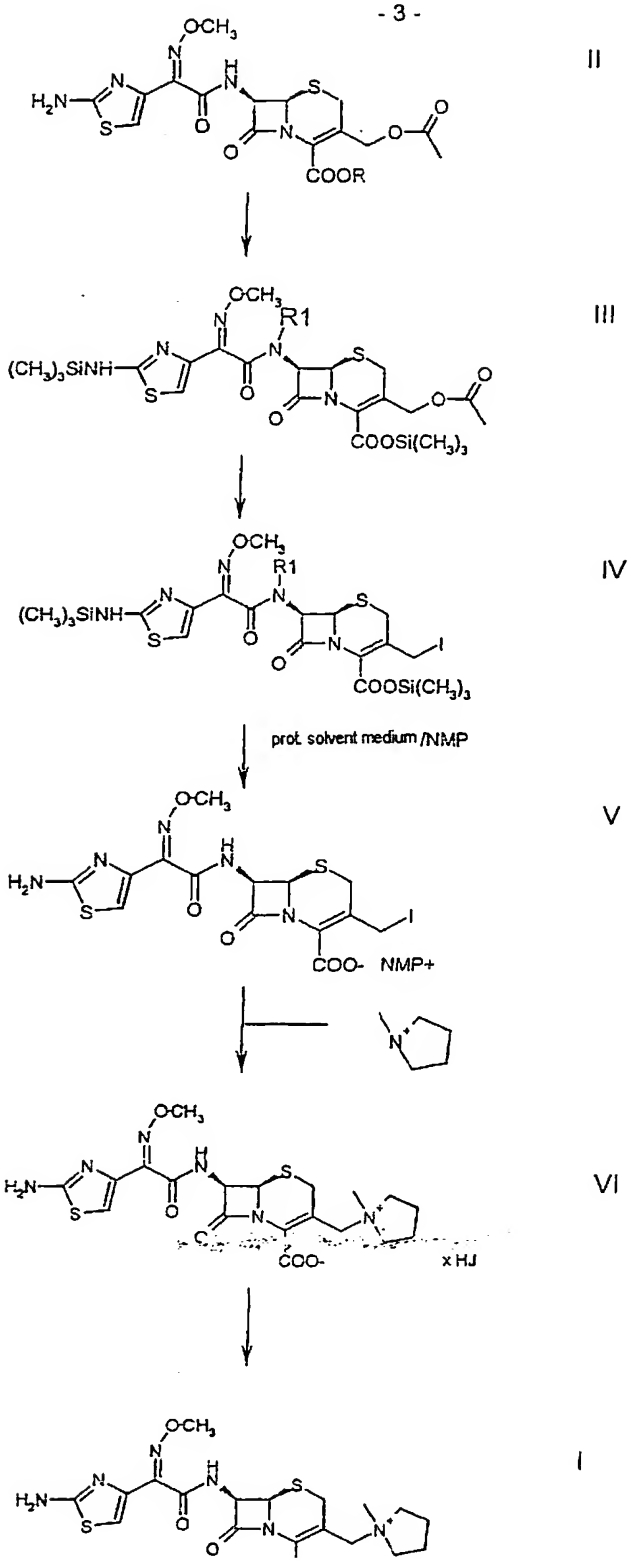


The choice of silylation agent is crucial to the smooth conversion of cefotaxime of the formula II in which R is hydrogen or sodium into a reactive, silylated derivative of formula III, wherein R1 signifies hydrogen or a trialkylsilyl group. Suitable silylation agents are iodotrimethylsilane in the presence of a non-nucleophilic base, N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA), (for example US patent 4,336,253); N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA) (for example EP 74 268); 1,1,1,3,3,3-hexamethyldisilazane (HMDS) or a combination of all the said silylation agents. The compound of formula IV is then produced in known manner with iodotrimethylsilane.

According to the above synthesis method, the silylated compound of formula IV is treated simultaneously with a protic solvent and N-methylpyrrolidone, wherein in the first step the compound of formula V is produced and this is then rapidly reacted with N-methylpyrrolidine. The reaction accordingly constitutes a desilylation reaction, followed by salt formation on the carboxylic acid and nucleophilic substitution. This principle simultaneously minimises the instability of the highly reactive iodomethyl grouping by an in situ reaction with N-methylpyrrolidine, and through the (desilylation) salt formation on the carboxylic acid, Δ2 formation is drastically reduced.

Suitable protic solvents are, in particular, alcohols, for example C_1-C_4-alcohols, preferred alcohols being ethanol and isopropanol. The amount of protic solvent is not critical, however it must be ensured that the reaction can proceed in a homogeneous solution or suspension, and, through insolubility, the compound of formula V is extracted from the possible further reaction in salt form or in free acid form.

In a preferred embodiment, the compound of formula IV is mixed with a mixture of N-methylpyrrolidine and alcohol, preferably isopropanol. In this way, not only does the above-described reaction sequence take place, but the title compound is obtained as an addition salt with hydroiodic acid. This can be isolated from the reaction mixture directly. The iodide is removed from the product simply by treatment in an aqueous or aqueous-organic solution, for example in a mixture of dichloromethane/water, with a commercial anion exchanger, for example with Amberlite LA-2, and by adding hydrochloric acid the active ingredient can subsequently be crystallised as the dihydrochloride hydrate according to known methods, for example from an aqueous/acetonic solution.

As an alternative, the isolated hydroiodide may be converted into the free zwitterion by known methods, for example by treatment with a trialkylamine in an organic solvent such as dichloromethane, and after isolation by methods known per se, this may can be converted into the title compound cefepime dihydrochloride hydrate.

The examples below elucidate the invention in more detail.

Example 1

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydriodide

100.0 g of cefotaxime are suspended in 1.2 l of methylene chloride and heated to reflux temperature. Whilst boiling under reflux, 2.5 ml of hexamethyl-disilazane (HMDS) and 0.2 ml of trimethyliodosilane are

added. Then, 102 ml of HMDS are added dropwise whilst stirring, and stirring is then effected at this temperature for 1 hour, and the resulting ammonia is removed by passing nitrogen into the reaction suspension. Then, the clear solution obtained is cooled to 10°C. 70 ml of trimethyliodosilane are added dropwise at this temperature. After stirring for 60 minutes, 10 ml of trimethyliodosilane are added dropwise, and after a further 30 minutes, a further 15 ml of trimethyliodosilane are added. After stirring for 165 minutes at 10°C, the reaction solution is stirred over the course of 2 minutes into a solution of 350 ml of N-methylpyrrolidine in 9 l of isopropanol, which solution has a temperature of 18°C. The resulting suspension is then stirred for 1 hour at room temperature. Then, it is filtered through a glass sintering filter and the filter cake is washed with 500 ml of isopropanol. After drying in a vacuum at room temperature, 97.7 g of the title compound are obtained in the form of a yellow coloured powder.

Example 2

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimimo)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate

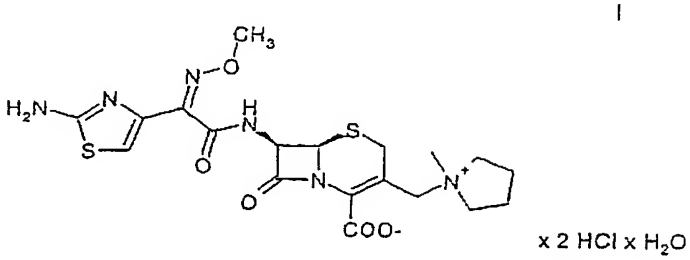
4.00 g of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)-methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydriodide are dissolved at room temperature in a mixture of 10 ml of H_2O and 30 ml of methylene chloride. The pH of the mixture is adjusted to 7.3 through the dropwise addition of ion exchanger LA-2. After stirring for 15 minutes, the phases are separated. The aqueous phase is adjusted to pH 2.5 with conc. hydrochloric acid and stirred for 15 minutes.

Then, the precipitate formed is separated by filtration. The clear filtrate is acidified to pH 1.0 with conc. hydrochloric acid and mixed with 1.6 g of activated carbon. After stirring for 10 minutes, the activated carbon is removed by filtration and the carbon cake is washed with 5 ml of H_2O. The filtrate and washing water are combined, acidified to pH 0.5 with conc. hydrochloric acid and diluted with 50 ml of acetone. Seed crystals are then added, and the resulting crystal suspension is stirred for ca. 20 minutes at room temperature. Subsequently, a further 50 ml of acetone is added dropwise over the course of 30 minutes. When the acetone addition is complete, the crystal suspension is cooled to 0°C. After stirring for 1 hour in an ice bath, the suspension is filtered and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.85 g of the title compound are obtained in the form of a white crystalline powder. Yield: 36.8%.

HPLC purity: > 99 area %

Claims

1. A process for producing the compound of formula I



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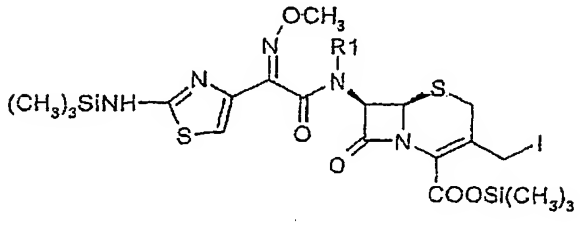
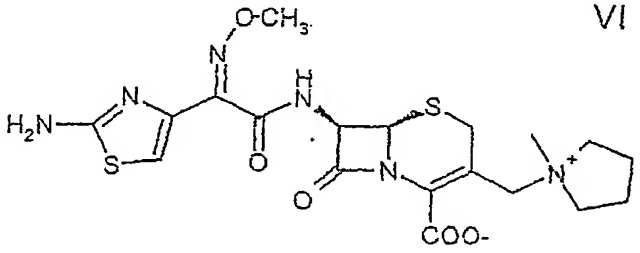
wherein a compound of formula IV



is desilylated in a protic solvent, and simultaneously reacted with N-methylpyrrolidine to form a compound of formula VI, and this is then converted into the compound of formula I

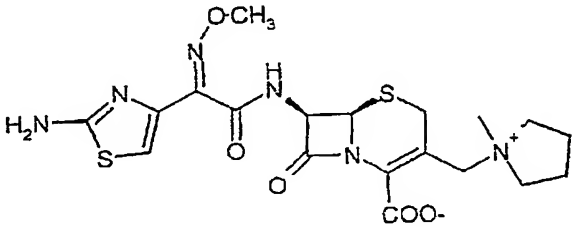


VI

2. A process as claimed in claim 1, wherein the protic solvent is a C_1-C_4-alcohol.

3. A process according to claim 1 or 2, wherein conversion of the compound of formula IV is effected using a basic ion exchanger.

4. A process as claimed in claim 1, 2 or 3, wherein conversion of the compound of formula VI into the compound of formula I is effected through the free betaine of formula VII in isolated form.



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Biochemie GmbH
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